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**When Sweet Turns Salty:
Glucose-induced Suppression of Atrial Natriuretic Peptide by MicroRNA-425**

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One of the most challenging aspects of obesity is its link to “metabolic syndrome,” when abdominal obesity is accompanied by high fasting blood glucose, low levels of high-density lipoprotein cholesterol, high levels of triglycerides, and elevated blood pressure. With rising obesity rates, metabolic syndrome is likely to become more common in the years ahead (1). Although progress has been made in identifying this syndrome’s individual components, their interplay across several organ systems is not well understood; that is, the near-linear relationship between body mass index and blood pressure. Obesity is often recognized as a predictor of treatment-resistant hypertension (2). One of the main endocrine pathways that has been implicated involves natriuretic peptides (3). Natriuretic peptides exert their antihypertensive effects predominantly by inducing natriuresis but have additional effects beyond blood pressure regulation. For example, an antihypertrophic effect, independent of blood pressure, was observed in the heart (4). Other reports demonstrate the ability of atrial natriuretic peptide (ANP) to promote lipolysis (5) and activate the brown fat thermogenic program (6). Notably, levels of natriuretic peptides are lower in obese subjects and patients with type 2 diabetes (7).

Genetic studies demonstrated that the single nucleotide polymorphism rs5068 (A/G) is most strongly associated with plasma ANP levels. Carriers of the minor G allele are less obese, have a lower risk of hypertension, and a decreased incidence of cardiovascular events (8). In this issue of the *Journal*, Arora et al. (9) expand upon their previous finding that the variant rs5068 (A/G) influences ANP production (10). *NPPA*, which encodes for ANP, is a target of micro ribonucleic acid (miRNA)-425 (miR-425). miR-425 is predicted to bind the sequence spanning rs5068 for the A, but not the G allele (Figure 1). Overexpression of miR-425 in human cardiomyocytes derived from induced pluripotent stem cells reduced *NPPA* messenger RNA and N-terminal (NT)-proANP protein levels (10).

In the present study, Arora et al. (9) explored miR-425 as a link between glycemia and ANP expression, thereby providing a potential explanation for lower NT-proANP plasma levels after food consumption (11). The authors demonstrated that: 1) a carbohydrate challenge lowered plasma ANP, but not brain natriuretic peptide; 2) high glucose increased miR-425 and decreased *NPPA* expression in human cardiomyocytes derived from embryonic stem cells; 3) a glucose stimulus enhanced

the transcription downstream of the miR-425 promoter in HepG2 cells, a human liver carcinoma cell line; and 4) miR-425 expression was nuclear factor kappa B (NF- κ B)–dependent in H9c2 cells, a rat cardiomyoblast cell line (Figure 1). Importantly, the human, but not the rodent, *NPPA* gene was a target of miR-425. By using transgenic mice carrying the human *NPPA* gene (*NPPA*^{tg/+} mice), the authors provided in vivo evidence for an inverse association of miR-425 and human *NPPA* expression in the right ventricle after glucose administration.

Key questions remain unanswered: Can inhibition of endogenous miR-425 attenuate the glucose-induced decrease in *NPPA* transcription or are miR-425–independent mechanisms responsible for regulating *NPPA* levels upon glucose stimulation? The latter could have been addressed by determining whether the endogenous mouse *NPPA* levels were unchanged after the glucose gavage. Moreover, miRNA targets can change depending on the cell context. Does inhibition of endogenous miR-425 result in a similar rise of ANP secretion in all cardiomyocyte-like cells? It remains unclear whether miR-425 is associated with cardiometabolic phenotypes in mice as observed by targeting other miRNAs (12). No data were included on metabolic parameters, blood pressure, and cardiac function of *NPPA*^{tg/+} mice.

A direct effect of endogenous miR-425 on ANP expression levels should have been confirmed in vitro and in vivo, to rule out a possible contribution by other miRNAs. For example, miR-103 and -107 are expressed in the heart (13), and are predicted to target the human *NPPA* gene. Expression levels of miR-103 and 107 are increased in livers of obese mice and regulate insulin sensitivity (14). A 20% to 30% increase of miR-425 expression was observed in the right atria and the right ventricles after *NPPA*^{tg/+} mice were gavaged with 2 g/kg glucose (9). The authors inferred that the concurring decrease of human *NPPA* expression in the right ventricle was the result of increased miR-425 levels, but presented no direct evidence that this modest change of miR-425 can account for the effects of glucose administration on *NPPA* expression.

Unlike ANP that is predominantly expressed in the atria, miR-425 expression was observed in several tissues, including liver and pancreas. MiR-425 expression levels in the myocardium are relatively low (15) and similar in atrial and ventricular tissues (10). The marked increase in ANP expression in cardiac tissue of heart failure (HF) patients (15) was associated with a compensatory rise in miR-425 levels

(Figure 2). Unloading by a left ventricular assist device reduced ANP levels in nonischemic HF patients with a corresponding reduction in miR-425 expression. Thus, in patients with advanced HF, miR-425-independent mechanisms appear to be at work, and miR-425 might fine tune, rather than determine, levels of ANP expression.

One of the recent landmark clinical trials in cardiovascular disease evaluated a neprilysin inhibitor, targeting the endopeptidase that degrades the natriuretic peptides (among others), which was chemically linked to an angiotensin receptor blocker (16). The impressive reduction of hospitalization for HF, as well as death from cardiovascular causes, might be explained, at least in part, by increasing ANP levels in the intervention group. Given this emerging new gold standard in clinical care, it is questionable whether miR-425 inhibitors would have therapeutic potential for raising ANP (10). Pharmacological modulation of miRNA expression can be successfully achieved (17). However, miRNA therapeutics face major challenges in that single base changes may profoundly affect toxicology, and off-target effects can occur due to the ubiquitous expression of most miRNAs. Also, there are difficulties in establishing the correct dosing regimen, demonstrating target engagement, and ensuring efficient delivery, in particular to the heart. Oligonucleotides tend to accumulate in the liver and the kidney. This build-up could become a concern during prolonged treatment for chronic conditions, such as metabolic syndrome.

In summary, Arora et al. (9) presented evidence for a mechanism whereby glucose intake induced miR-425 expression, which in turn decreased ANP levels, potentially contributing to hypertension and other deleterious effects in cardiometabolic disease. Although a definitive pathophysiological link between miR-425, obesity, diabetes, and ANP levels is not yet established, this study does add to the compelling evidence that miRNAs are part of important regulatory mechanisms in cardiometabolic diseases that merit further investigation (18).

DISCLOSURES

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KEY WORDS

Cardiometabolic; cardiomyocytes; obesity; transcription

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FIGURE LEGENDS

Figure 1. Association of miR-425 With ANP

(A) In the base pairing between microribonucleic acid 425 (miR-425) and the 3' untranslated region (3' UTR) of human *NPPA*, the red box indicates the seed sequence (position 2 to 8). Yellow = variants of rs5068. (B) The in vitro and in vivo effects as observed in the study by Arora et al. [\(9\)](#). DNA = deoxyribonucleic acid; hESC-CM = human embryonic stem cell–derived cardiomyocyte; NF = nuclear factor; NT-proANP = N-terminal pro-atrial natriuretic peptide; RA = right atrium; RNA = ribonucleic acid; RV = right ventricle.

Figure 2. MiR-425 and ANP Levels in Cardiac Tissue

Atrial natriuretic peptide (ANP) (A) and microribonucleic acid 425 (miR-425) (B) expression levels were determined by deep RNA sequencing of cardiac tissue from nonfailing (NF) patients, from patients with ischemic cardiomyopathy (ICM), and from patients with nonischemic cardiomyopathy (NICM) pre- and post-left ventricular assist device (LVAD) implantation, respectively [\(15\)](#). * $p < 0.05$, ** $p < 0.01$ compared with NF patients. Reprinted with permission of Wolters Kluwer Health, Inc.

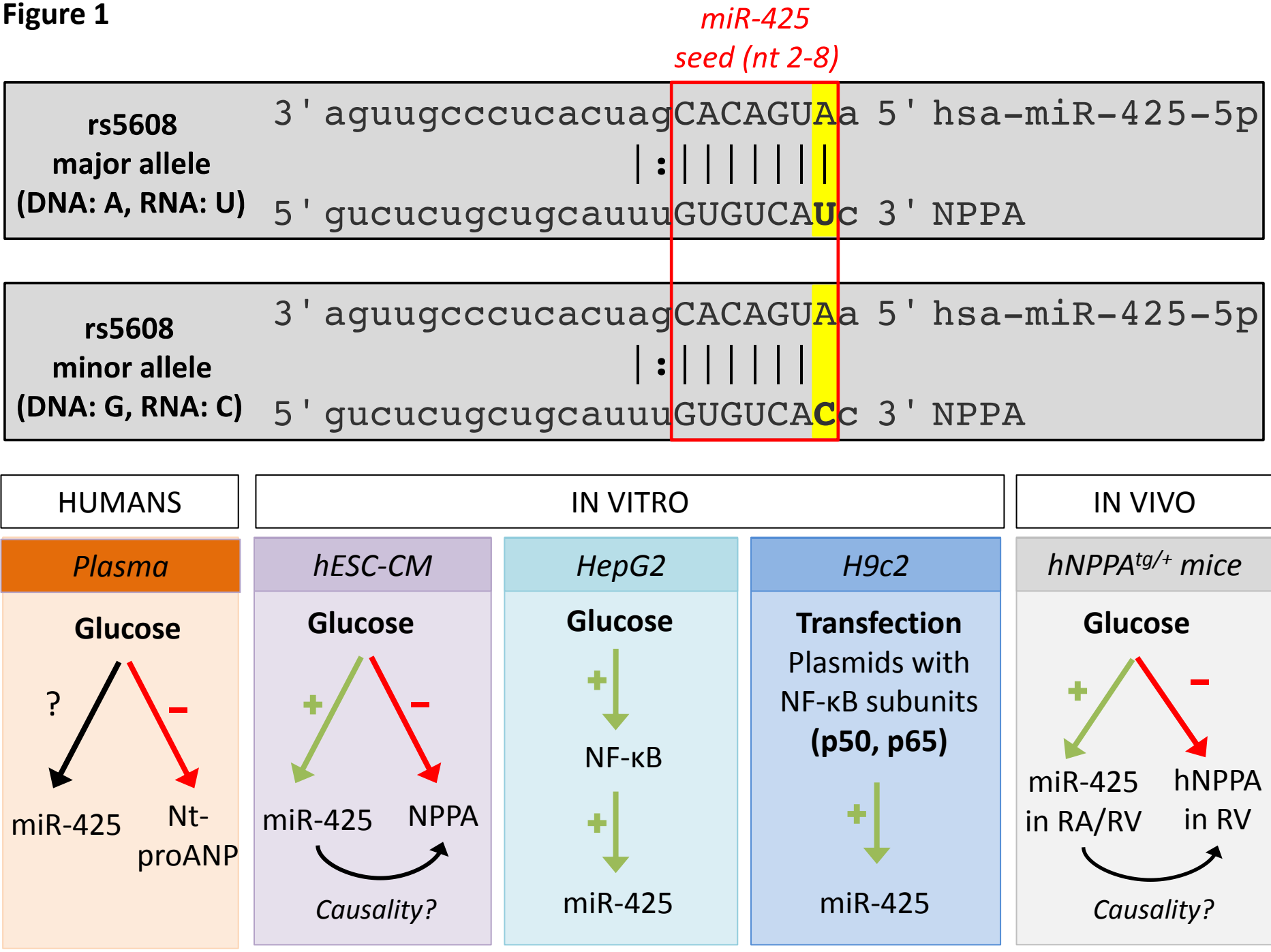


Figure 2

